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### REMARKS

Claims 1-30 are presently pending and under examination. Claims 3, 4, 5, 10 and 11 have been amended herein. New claims 33 and 34 have been added.

Claims 3, 4 and 5 have been amended by replacing the term "sequencing primer" with the proper term "sequence primer" used in the corresponding base claim (claim 1). This amendment merely corrects a typographical error and makes clear the antecedent basis in claim 1. No new matter is added by the amendment.

Claim 10 has been amended to recite that the microspheres are distributed "at discrete sites." The amendment is supported throughout the specification, for example, by claim 18 as originally filed. No new matter is added by the amendment.

Claim 11 has been amended to change the term "said capture probe" to "a capture probe" to acknowledge that this claim element is added by claim 11 and does not have antecedent basis in base claim 10. Claim 11 has further been amended to omit recitation of the terms "an adapter probe" and "said target sequence." Keeping with the *one claim, one element rule* for dependent claims, the element of the adapter probe has been added via new dependent claim 33. No new matter is added by the amendment to claim 11 or new claim 33.

Finally, new claim 34 has been added, which is directed a method of sequencing a genome by amplifying a genome, thereby obtaining a plurality of target nucleic acids each comprising a first domain and an adjacent second domain, where the second domain includes a plurality of target positions; subsequently providing an array encompassing a substrate with a surface comprising discrete sites; and a population of microspheres comprising at least a first and second subpopulation, distributed at the discrete sites; hybridizing sequencing primers to the first domains of the target sequences, wherein the hybridization complexes are attached to the microspheres; simultaneously extending the primers by the addition of a first nucleotide to a first detection position using a first enzyme to form an extended primer; and detecting the release of pyrophosphate (PPi) to determine the type of the first nucleotide added onto the primers; and determining the identity and location of the microspheres. Support for "sequencing a genome" and step (a) can be found, for example, at page 1, lines 23-25; page 5, lines 32-36; page 6, lines

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3-7; page 8, lines 7-9; the paragraph spanning pages 49-50. Support for the remainder of the claim can be found in claim 1 as originally filed and in the sections of the specification previously cited in Applicants' response filed 2/20/03, at page 5, first paragraph.

No new matter is added by the amendments to claims 3, 4, 5, 10 and 11, nor by new claims 33 and 34. Entry of the amendments and new claims is respectfully requested.

**Rejections under 35 U.S.C. § 112, second paragraph**

The rejection of claims 3-5, 11, 12, and 25-27 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention, respectfully is traversed. Applicants submit that claims 3-5, 11, 12, and 25-27 are clear and definite to one possessing the ordinary level of skill in the art in view of the specification.

The Office Action asserts that claims 3, 4, and 5 recite the term "said sequencing primer" while the corresponding base claim recites the term "sequence primer." This rejection is rendered moot by the above-proposed amendment to claims 3, 4, and 5, which are amended to each recite the term "sequence primer" rather than "sequencing primer." Accordingly, Applicants respectfully request withdrawal the rejection of claims 3, 4, and 5, under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention

The Office Action asserts that claims 11 and 12 lack antecedent for the claim term "capture probe" in their corresponding base claim. This rejection is rendered moot by the above-proposed amendment, which amends claims 11 to recite "a capture probe" indicating that this claim element is first introduced into the claim lineage. Accordingly, Applicants respectfully request withdrawal the rejection of claims 11 and 12, under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

The Office Action asserts that claims 25 lacks antecedent for the claim term "discrete sites" in its corresponding base claim. This rejection is rendered moot by the above-proposed amendment, which amends base claim 10 to recite "discrete sites," thereby providing

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proper antecedent basis for this claim term. Accordingly, Applicants respectfully request withdrawal the rejection of claims 25-27, under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

### **Rejections under 35 U.S.C. § 103(a)**

Applicants respectfully traverse the rejection of claims 1-4, 6-10, 12-17, and 22-27 as allegedly obvious under 35 U.S.C. § 103(a) over Navot et al., United States Patent No.6,335,165, and Walt et al., United States Patent No. 6,327,410.

The Office Action asserts, at page 6, first paragraph, that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used microspheres randomly distributed on a surface of Walt et al. in the pyrosequencing method allegedly described by Navot et al. The motivation necessary to combine the references, alleged to be expressly provided by Walt et al., would have been that synthesis of nucleic acids was separated from their placement on the array and random distribution of beads was inexpensive. Applicants respectfully disagree with the assertion that either of the cited references disclose the desirability for making a combination that is Applicants' claimed invention.

The Navot et al. patent is directed to methods and kits of characterizing a GC rich region of a nucleic acid of interest, which is described as being derived from an individual to be diagnosed and as being genomic DNA or RNA (see Abstract, column 10, lines 17-19). The Navot et al. patent does not disclose large scale sequence determination involving a plurality of target nucleic acids. Walt et al. is directed to compositions encompassing a substrate with a surface comprising discrete sites, and a population of microspheres distributed on the sites. The microspheres can include subpopulations of bioactive agent and corresponding optical signatures capable of identifying the corresponding bioactive agent (see Summary of the Invention)..

To establish a *prima facie* case of obviousness, the Office must show that the prior art would have suggested the claimed method to one of ordinary skill in the art and that it could have been carried out with a reasonable likelihood of success when viewed in the light of

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the prior art. *Brown & Williamson Tobacco v. Philip Morris*, 229 F.3d 1120, 1124 (Fed. Cir. 2000).

For the reasons set forth below, the assertion that it would have been obvious for one skilled in the art to combine the cited references to arrive at Applicants' claimed invention is not accompanied by the required showing of where the cited references disclose the desirability of making the specific combination that is Applicants' claimed invention. Establishing that the prior art would have suggested the claimed method requires an underlying factual showing of a suggestion, teaching, or motivation to combine the prior art references and is an "essential evidentiary component of an obviousness holding." *Brown & Williamson Tobacco*, 229 F.3d at 1124-25 (quoting *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1351-52 (Fed.Cir.1998); see also *C.R. Bard* at 1351 (obviousness requires some suggestion, motivation, or teaching in the prior art where to select the components that the inventor selected and use them to make the new device); *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000) (there must be some motivation, suggestion or teaching in the prior art of the desirability of making the specific combination that was made by the applicant). The evidentiary showing must be clear and particular and broad conclusory statements about the teachings of the cited references, standing alone, are not "evidence." *Brown & Williamson Tobacco*, 229 F.3d at 1125 (quoting *In re Dembiczak*, 175 F.3d 994, 1000 (Fed.Cir.1999), *abrogated on other grounds by In re Gartside*, 203 F.3d 1305, 53 USPQ2d 1769 (Fed.Cir.2000)).

Moreover, reliance on "common knowledge and common sense" to fill the void for the required showing of a suggestion for a claimed combination of elements does not substitute for the obligation to cite references to support an obvious conclusion. *In re Thrift*, 298 F.3d 1357, 1364 (Fed. Cir. 2002). Consequently, such a lack of an evidentiary showing is nothing more than impermissible hindsight reconstruction based on reading Applicant's own invention and reliance on unsupported conclusory statements.

In the current Office Action, there has been no underlying factual showing that it would have been obvious to one of ordinary skill in the art to have modified the cited references by Navot et al. and Walt et al. to obtain the specific combination of elements of the claimed invention. The alleged motivation provided by Walt et al. is that synthesis of nucleic acids was separated from their placement on the array and random distribution of beads was inexpensive.

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Applicants respectfully submit that the underlying statement, which is found at column 4, lines 43-48, does not provide a motivation to combine the disclosures of Walt et al. and Navot et al. In context, the passage of Walt et al. reads as follows:

This allows the synthesis of the bioactive agents (i.e. compounds such as nucleic acids and antibodies) to be separated from their placement on an array, i.e. the bioactive agents may be synthesized on the beads, and then the beads are randomly distributed on a patterned surface. Since the beads are first coded with an optical signature, this means that the array can later be "decoded", i.e. after the array is made, a correlation of the location of an individual site on the array with the bead or bioactive agent at that particular site can be made. This means that the beads may be randomly distributed on the array, a fast and inexpensive process as compared to either the in situ synthesis or spotting techniques of the prior art. Once the array is loaded with the beads, the array can be decoded, or can be used, with full or partial decoding occurring after testing, as is more fully outlined below.

Walt et al., column 4, lines 44-59.

The context of the statements relied upon by the Examiner is a comparison of methods for synthesizing random and spotted arrays. Applicants respectfully submit that the Walt et al. patent, would not have motivated the skilled artisan familiar with the Navot et al. patent to combine the two references, since Navot et al. is directed to the sequence determination of a particular GC-rich nucleic acid of interest derived from an individual to be diagnosed rather than a plurality of target nucleic acid sequences regardless of their base composition. Consequently, the alleged express motivation of Walt et al. would not have provided such an impetus to the skilled artisan familiar with the Navot et al. patent. Without such motivation to combine, the present rejection is unsupported by the cited references.

In view of the above arguments, Applicants respectfully request removal of the rejection of claims 1-4, 6-10, 12-17, and 22-27 as allegedly obvious under 35 U.S.C. § 103(a) over Navot et al., United States Patent No. 6,335,165, and Walt et al., United States Patent No. 6,327,410.

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Applicants further respectfully traverse the rejection of claims 5 and 11, as allegedly obvious under 35 U.S.C. § 103(a) over Navot et al., *supra*, and Walt et al., *supra*, and further in view of Balch et al., United States Patent No. 6,083,763.

The patent by Balch et al. is cited as a further secondary reference merely for allegedly disclosing adapter probes, which are recited in claims 5 and 11. As set forth above, a lack of motivation exists to combine Navot et al. and Walt et al. to arrive at Applicants' claimed invention. This deficit is not cured with regard to claims 5 and 11 by further citation of the Balch et al. patent. In addition, nothing in the Balch et al. reference would have provided a motivation to the skilled artisan to combine this reference with Navot et al., *supra*, and Walt et al., *supra*.

The alleged express motivation, which is described at page 7, first partial paragraph, of the Office Action as adapter probes providing a unique binding domain for each site on an array is merely a conclusory statement. This statement of express motivation falls short of representing the essential evidentiary component required by the Federal Circuit for an obviousness showing, which must include a factual showing of a suggestion, teaching, or motivation to combine the prior art references to arrive at each element of the claimed invention. Given the initial lack of motivation described above with regard to combining Navot et al., *supra*, and Walt et al., *supra*, the statement that adapter probes provide a unique binding domain for each site on an array also does not provide motivation to combine Balch et al. with Navot et al., *supra*, and Walt et al., *supra*, to arrive at the claimed invention of claims 5 and 11.

In view of the above arguments, Applicants respectfully request removal of the rejection of claims 5 and 11 as allegedly obvious under 35 U.S.C. § 103(a) over Navot et al., *supra*, and Walt et al., *supra*, and further in view of Balch et al., United States Patent No. 6,083,763.

Applicants further respectfully traverse the rejection of claims 18-21 and 28-30, as allegedly obvious under 35 U.S.C. § 103(a) over Navot et al., *supra*, and Walt et al., *supra*, and further in view of Nyren et al., WO 98/13523.

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The international patent publication by Nyren et al. is cited at page 7, final paragraph, of the Office Action as a further secondary reference merely for allegedly disclosing kits encompassing a sequence primer, a polymerase, a detection enzyme means for identifying pyrophosphate relief, dNTPs pr ddNTPs. As set forth above, a lack of motivation exists to combine Navot et al. and Walt et al. to arrive at Applicants' claimed invention. This deficit is not cured with regard to claims 18-21 and 28-30 by further citation of the Nyren et al. patent publication. In addition, nothing in the Nyren et al. publication would have provided a motivation to the skilled artisan to combine this reference with Navot et al., *supra*, and Walt et al., *supra*.

With regard to Nyren et al., the Office Action, at page 8, first paragraph, describes as necessary motivation that "kits were conventional in the field of molecular biology and provided the benefits of convenience and cost-effectiveness." Rather than providing the necessary showing of a motivation to combine, this statement is conclusory, thus falling short of representing the essential evidentiary component required, which must include a factual showing of a suggestion, teaching, or motivation to combine the prior art references to arrive at each element of the claimed invention. Given the initial lack of motivation described above with regard to combining Navot et al., *supra*, and Walt et al., *supra*, the statement that kits were conventional in the field of molecular biology and provided the benefits of convenience and cost-effectiveness does not provide motivation to combine Nyren et al. with Navot et al., *supra*, and Walt et al., *supra*, to arrive at the claimed invention of claims 18-21 and 28-30.

In view of the above arguments, Applicants respectfully request removal of the rejection of claims 18-21 and 28-30, as allegedly obvious under 35 U.S.C. § 103(a) over over Navot et al., *supra*, and Walt et al., *supra*, and further in view of Nyren et al., WO 98/13523.

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**CONCLUSION**

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to contact the undersigned attorney or Cathryn Campbell with any questions related to this application.

Respectfully submitted,

A handwritten signature in black ink, reading "Astrid R. Spain", written over a horizontal line.

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